REMARKS

By the present communication, no claims are amended. Claims 47-56 are currently pending and under examination. Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

Claim Rejections – 35 U.S.C. § 103(a)

In the Office Action, claims 47-56 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Vockley *et al.* (U.S. 6,316,199, herein "Vockley") and Clark *et al.* (WO 02/44360, herein "Clark") in view of Mehvar *et al.* (*J Pharm Pharmaceut Sci* 3(1): 125-136, 2000, herein "Mehvar") and Takaku *et al.* (*Int J Cancer* 51(2):244-9, 1992, herein "Takaku"). Applicants respectfully traverse the rejection.

As emphasized by the Supreme Court in *KSR,* in determining obviousness based on a combination of references, the central issue is whether the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *See KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385, 1396 (2007) and MPEP 2143.02. The fact that the references can be combined is insufficient to establish obviousness if one of ordinary skill in the art could not reasonably predict the result of that combination. In this case, Applicants submit that the cited references do not provide any reasonable basis to predict that administering a modified, full-length recombinant human Arginase I to a patient could treat a human liver, breast, colon or rectal malignancy. In fact, for the reasons detailed below, a careful reading of the references would suggest to one of ordinary skill in the art that Arginase I would not be effective for the treatment of liver, breast, colon or rectal cancer. Thus, the present ground of rejection should be withdrawn.

A. The teachings of Vockley have been misapprehended because Vockley does not teach pharmaceutical compositions for treating cancer.

In the Office Action, the Examiner states that Vockley teaches pharmaceutical compositions for treating cancer. According to the Office,

> Vockley et al. teach human arginase II and I, wherein said arginase I is 100% identical to arginase I of SEQ ID BNO: 9 [*sic*] of the instant application, which degrades arginine to ornithine and urea, resulting in reducing the arginine level, and a method for treating human cancer including prostate cancer by administering arginase II polypeptide (see Col 3, line 37-38).

(Office Action, pp. 3-4). Applicants respectfully submit that the teachings of Vockley have been misapprehended. Vockley does not teach a method of treating cancer using Arginase II. Rather, Vockley teaches using Arginase II polypeptides "to treat diseases associated with or caused by as a defect in the Arginase II gene or Arginase II gene expression, such as, for example ... prostate disease, particularly prostate cancer." (col. 2, lines 35-46). Vockley lacks any teaching or suggestion of using Arginase II to treat cancer generally. The instant claims are not directed to the treatment of prostate cancer, and Vockley does not indicate that human liver, breast, colon, or rectal malignancies are associated with or caused by a defect in the Arginase II gene or Arginase II gene expression. Thus, Vockley lacks any teaching or suggestion of using Arginase II—let alone Arginase I—for the treatment of human liver, breast, colon, or rectal malignancies. Because Vockley fails to teach or suggest all elements of the independent claims, and this deficiency is not cured by any of the secondary references, a *prima facie* case of obviousness cannot be established.

B. Vockley teaches away from using recombinant arginase I for the treatment of cancer.

When the data in Vockley is examined closely, one of skill in the art would understand that Vockley teaches away from administering either Arginase I or Arginase II polypeptides for the treatment of cancer. In Example 8, Vockley measured the arginase activity in solid tumor samples and normal adjacent tissues (col. 41, lines 21-39). The investigators found that arginase activity was increased in the cells of breast, ovarian, lung, colon, testicular, and prostate tumors. Vockley further measured the serum arginase activity in a number of different cancer patients. They found that arginase activity is present at high levels in the sera of metastatic cancer patients (*See* Table 2). According to Vockley,

> All of these data suggest that arginase expression and activity may be a key factor in the formation and metastasis of cancer. As arginase depletes the arginine concentration within the cell, it shuts down nitric oxide synthesis disabling tumor-infiltrating macrophage and limiting the cytotoxic effect of nitric

> oxide. At the same time, polyamine synthesis may be stimulated by the production of large amounts of ornithine, the end product of the arginase reaction, through ornithine decarboxylase, while proline biosynthesis is enhanced through the action of ornithine aminotransferase on the excess ornithine. The effect of elevated arginase activity in the serum is to have a systemic interference with the immune system to include inhibiting lymphocytes and three different splenic derived killer cells. Combined, there is a stimulation of cancer growth while at the same time a local and systemic inhibition of the immune system.

(col. 42, lines 21-36, emphasis added). Vockley suggests that increased arginase activity and depletion of arginine in cancer cells and in the serum may lead to the progression of disease. According to Vockley's hypothesis, the administration of either Arginase I or Arginase II to cancer patients would not be indicated for the treatment of cancer because the level of arginase is already elevated in these patients. Thus, one of skill in the art would expect that administration of arginase to cancer patients would have significant detrimental effects.

Contrary to this expectation, the present inventors have demonstrated that depletion of arginine to below 10 μM for at least three days by administering a modified, full-length recombinant human Arginase I polypeptide effectively treated malignancies in human and animal subjects (*See* Examples 12 and 15-18). This was a surprising result that does not predictably follow from the teachings of Vockley. According to the M.P.E.P. § 2145, "The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986)." The present inventors proceeded contrary to Vockley's teachings to demonstrate that modified, recombinant Arginase I may be used for the treatment of human liver, breast, colon or rectal cancer. For at least this reason, the present claims are not obvious in view of the cited references.

C. Takaku also teaches away from using arginase for the treatment of cancer.

The Office asserts that it would have been obvious to substitute arginase I or arginase II in methods for treating cancer because Takaku teaches that administering an arginine degrading enzyme, such as arginine deiminase, to a subject could reduce the arginine level to around 5 μM for 3 days (Office Action, p. 6). However, Takaku only showed that arginine deiminase exhibits

anti-tumor activity. Takaku provided no evidence that other arginine-degrading enzymes could be used in place of arginine deiminase, and explicitly stated that arginase would not be effective because it would not possess sufficient *in vivo* activity to produce anti-tumor effects. According to Takaku, arginase "has not been applied to the treatment of human cancer because of its poor antitumor activity *in vivo*." (Takaku, p. 244, left column, second paragraph). Takaku further states that

> The chemotherapeutic effectiveness of amino-acid degrading enzymes depends on some enzymatic properties such as the Michaelis constant (K_m), specific activity, optimum pH and stability, as well as the susceptibility of target tumor cells to lack of specific amino acids. For example, human liver arginase has a K_m value for L-arginine of 10.5 mM. The K_m value seems too high to exert enough enzyme activity in human blood, in which the normal L-arginine level is about 0.1 mM. Indeed, its *in vivo* growth-inhibitor activity is very weak or non-existent....

(Takaku, p. 249, left column, first full paragraph, emphasis added). Takaku clearly indicates that not all arginine-degrading enzymes are equivalent and it cannot be predicted which enzymes have sufficient *in vivo* activity to be effective for the treatment of various human malignancies. For this reason, it could not have been predicted with a reasonable expectation of success that human arginase I could be substituted for either arginase II or arginine deminiase in methods for treating cancer.

The test for obviousness is what the combined teachings of the pertinent prior art references would have suggested to one of ordinary skill in the art. See MPEP 2143.01. Thus, a prior art reference teaching disadvantages that lead away from the claimed invention must impact the obviousness analysis. *See U.S. v. Adams*, 383 U.S. 39, 52 (1966). Because Takaku teaches that not all arginine-degrading enzymes possess equivalent *in vivo* activity, one of skill in the art would not have a reason to modify or combine the references in the way alleged by the Office. As such, a *prima facie* case of obviousness cannot be established.

D. The secondary references fail to cure the deficiencies of either Vockley or Takaku.

Applicants respectfully submit that the additional secondary references cited by the Office in no way overcome the essential deficiency of the primary references discussed above. The

Office relies on Clark for teaching a modified arginine deiminase for treating cancer. Mehvar is relied on for teaching a PEG-modified arginase protein. However, these references do not teach or suggest a method of administering a PEG-modified, full-length recombinant human arginase I to a patient for the treatment of a human liver, breast, colon or rectal malignancy. Accordingly, these references cannot cure the fundamental defect in either the Vockley or Takaku references mentioned above, and a *prima facie* case of obviousness cannot be established.

E. Conclusion.

As discussed above, the methods of the invention relate to administering a PEG-modified, full-length recombinant human arginase I to a patient for the treatment of a human liver, breast, colon or rectal malignancy. Vockley and Takaku suggested that such a method would not be effective. As such, the combined references fail establish a *prima facie* case of obviousness for the claimed methods. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 103.

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Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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By _____

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